REMARKS

Status of the Claims

Claims 1-20 have been rejected. Claims 1-20 remain pending.

The Rejection of the Claims Under 35 U.S.C. §103 Should Be Withdrawn

The rejection of claims 1-20 under 35 U.S.C. §103 was maintained in view of Gee *et al.* (RE 35,517); Roof *et al.* (1994) *Experimental Neurology 129*:64-69; Roof *et al.* (1992) *Restorative Neurology and Neuroscience 4*:425-427; and Roof *et al.* (1997) *Molecular and Chemical Neuropathology 31*:1-11 and further in view of U.S. Patent No. 5,068,226. This rejection is respectfully traversed.

1. The teachings of each of the cited references have been made of record in the declaration filed under 37 C.F.R. 1.132 on December 19, 2003. The 132 declaration further addressed inaccurate scientific conclusions being drawn to assemble the 103 rejection. In the April 21, 2004 Office Action, the Examiner dismisses the evidence provided in the 132 declaration for two reasons. First, the Examiner asserts that the 132 declaration "fails to set forth any factual evidence." The Examiner has not pointed to any specific examples in the declaration to support this conclusion. Applicant maintains that the evidence provided in the 132 declaration presents scientific facts that rebut the various assertions being drawn throughout the obviousness rejection. The Examiner's attention is drawn to MPEP 716.01 which states:

> Where the evidence [of a declaration filed under 37 C.F.R. 1.132] is insufficient to overcome the rejection, the examiner must specifically explain why the evidence is insufficient. General statements ... without an explanation supporting such findings are insufficient.

Accordingly, if the Examiner continues to dismiss the factual evidence provided in the 132 declaration, a detailed explanation of the defects appearing in the declaration is respectfully requested.

Second, the Examiner asserts that the 132 declaration discusses the possible mechanism of action of allopregnanolone and progesterone and states that "the mechanism of action of

treatment does not have a bearing on the patentability of the invention ..." The discussion of the mechanism of action of allopregnanolone and progesterone appears in the 132 declaration because, in formulating the 103 rejection, the Examiner repeatedly asserts that progesterone and its metabolites, such as allopregnanolone, are known to share the same mechanism of action. The 132 provides factual evidence to rebut these assertions.

The Examiner is respectfully requested to reconsider the 132 declaration filed on December 19, 2004 in view of the following remarks.

II. A *prima facie* case of obviousness requires a motivation to combine the references. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills*, 16 USPQ 2d1430 (Fed. Cir. 1990). The cited art fails to satisfy this requirement.

First, in providing motivation to combine the cited references, the Examiner continues to assert that "allopregnanolone is also known to possess higher potency and efficacy than progesterone" based on the teachings of Gee *et al.* (page 5, lines 14-16 of the Office Action mailed April 21, 2004). Applicants continue to disagree with this assertion. As outlined in section 4a of the 132 declaration, Gee *et al.* teach that both progesterone and many of its metabolites bind with high affinity to a unique GABA/GBR complex and that these metabolites delay onset of myoclonus following TBPS induced seizures in mice. *There is no data demonstrating that progesterone and allopregnanolone are effective at treating other disease states*, such as traumatic brain injury, and certainly no teaching that *all* of progesterone's beneficial effects are related to progesterone's conversion into its various metabolites.

Second, in providing motivation to combine the cited references, the Examiner continues to assert that, "progesterone and its metabolites such as allopregnanolone are known to share the same mechanism of action on their neuroprotective effects through their interaction with GABA" (page 5, lines 14-16, Office Action mailed April 21, 2004). This conclusion is not supported by the cited art. As previously made of record, *the Examiner has failed to satisfy the requirements of MPEP 2144.02 and 2144.03 and provide evidence for these conclusions*. In an effort to expedite prosecution, the 132 declaration filed on December 19, 2004 addressed this assertion. The Examiner's attention is drawn to sections 4b, 4c, 4d, and 4e of the 132 declaration that

outlines that the mechanism of action by which progesterone and allopregnanolone mediate their neuroprotective effects is unknown and further concludes that one of skill would not assume that progesterone and allopregnanolone have identical mechanisms of action. Moreover, the previously submitted 132 declaration further provides evidence that the mere assumption that compounds with similar precursors or structures have identical mechanisms of action is flawed. See, section 4c. In fact, the 132 declaration provides 4 lines of evidence for this conclusion, supported by several scientific references provided as Appendices.

Third, in providing motivation to combine the cited reference, the Examiner asserts that Roof *et al.* (1997) teaches that "progesterone's neuroprotective effects are through its interaction with GABA, and progesterone and some of its metabolites are known to bind to and potentiate activity of GABAa receptor" (page 4, first paragraph and page 5, lines 15-20, Office Action mailed April 21, 2004). As previously made of record, these conclusions are not scientifically accurate. The declaration filed on December 12, 2003 clarified the teachings of Roof *et al.* (1997). Specifically, sections 4b and 4c of the declaration clearly demonstrates that the neuroprotective effects of progesterone remain unknown and could act via several biological mechanisms. Roof *et al.* (1997) speculate that progesterone could act via "radical scavenging and membrane stabilization" (page 7, paragraph 2), could interact with GABAa receptor, and/or antagonize the glutamate receptor system (page 7, paragraph 3). Roof *et al.* all never concludes progesterone's neuroprotective activity results from *only* GABA receptor modulation.

Again, a traumatic central nervous system injury does not simply disrupt the GABA receptor system. A traumatic injury to the central nervous system leads to *a cascade of physiological events that lead to neuronal loss.* This point is again expressed in the specification on page 5, lines 8-15 that clearly states that "a traumatic injury to the CNS results in *multiple physiological events* that impact the extent and rate of neurodegeneration and thus the final outcome of the injury". Modulation of only the GABA receptor provides no assurances that one could treat a traumatic central nervous system injury as asserted in the Office Action.

Fourth, the Examiner has further maintained that there is motivation to combine the cited references by asserting that allopregnanolone and progesterone have the "the same therapeutic usefulness" (page 5, last paragraph, and page 6, lines 1 and 2 of the April 21, 2004 Office Action). This conclusion is not supported by the cited art. Again, the Examiner has failed to

satisfy the requirements of MPEP 2144.02 and 2144.03 and provide evidence for this conclusion. In an effort to expedite prosecution, Applicants responded to these assertions in the 132 declaration filed on December 19, 2003. Specifically, the Examiner's attention is drawn to sections 4e of the 132 declaration that outlined that the mechanism of action by which progesterone and allopregnanolone mediate their neuroprotective effects is unknown and further concludes that one of skill would not assume progesterone and allopregnanolone have identical mechanisms of action.

In providing motivation to combine Roof *et al.* and Gee *et al.*, the Examiner continues to equate the neuroprotective effects of progesterone following a traumatic CNS injury with modulating GABA. As previously made of record, this conclusion is inaccurate. Applicants note that the Examiner has failed to provide evidences for this assertion as required by MPEP 2144.02 and 2144.03. In an effort, to expedite prosecution, this issue was addressed in the accompanying 132 declaration. Specifically, the Examiner's attention is drawn to sections 4b and 4f of the declaration that demonstrates that modulating GABA is not equivalent to treating a traumatic brain injury.

Applicants again clarify that a traumatic injury to the CNS is *not* the disruption of the GABA system, but rather, as indicated on page 2, lines 28 and page 3, lines 3 of the specification, a traumatic injury to the central nervous system leads to *a cascade of physiological events that lead to neuronal loss.*

> Following a traumatic injury to the central nervous system, *a cascade of physiological events* leads to neuronal loss including, for example, an inflammatory immune response and excitotoxicity resulting from the initial impact disrupting the glutamate, acetylcholine, cholinergic, $GABA_A$, and NMDA receptor systems. In addition, the traumatic CNS injury is frequently followed by brain and/or spinal cord edema that enhances the cascade of injury and leads to further secondary cell death and increased patient mortality. (emphasis added)

This point is again expressed in the specification on page 5, lines 8-15 that clearly states "a traumatic injury to the CNS results in *multiple physiological events* that impact the extent and rate of neurodegeneration and thus the final outcome of the injury."

The prior art itself must provide the skilled artisan the motivation to make the claimed invention. As traumatic injury to the central nervous system leads to *a cascade of physiological events that lead to neuronal loss*, one of skill in the art would not equate modulating activity of the GABA receptor with successful treatment of a traumatic injury to the CNS. Accordingly, one of skill would not be motivated to combine the teachings of Gee *et al.* and Roof *et al.* Applicants continue to maintain the claims of the present invention are being used as a guide to select references at random that mention various aspects of the claimed invention. None of the cited references would guide one of skill in the art to select allopregnanolone, *among the multitude of progesterone metabolites*, and administer this compound to a subject having a *traumatic CNS injury*. As there is no basis in the art for combining or modifying the cited references, a *prima facie* case of obviousness has not been established.

III. A *prima facie* case of obviousness further requires the cited prior art to provide a reasonable expectation of success. As previously made of record, the cited art fails to provide a reasonable expectation that the administration of allopregnanolone to a subject would successfully treat a *traumatic* CNS injury or decrease neurodegeneration following a *traumatic* CNS injury as claimed by the instant invention. First, the guidance provided by the cited art must be sufficiently specific to direct the attention of one skilled in the art to the selection of parameters and choices necessary to obtain the claimed invention. None of the references cited demonstrate or suggest the administration of allopregnanolone to treats a *traumatic* CNS injury or decrease neurodegeneration following a *traumatic* CNS injury as claimed by the instant invention. The art therefore fails to inherently or explicitly suggest the administration of allopregnanolone to a subject having a *traumatic* (*i.e.*, physical force) CNS injury.

Moreover, the initial impact of a traumatic injury to the CNS produces many physiological events, including the disruption of multiple receptors/neurotransmitters. Therefore, modulating the activity of a single receptor as taught by Gee *et al.* is hardly sufficient to provide a reasonable expectation that allopregnanolone would successfully treat the traumatic CNS injury as claimed by the instant invention. See, sections 4c and 4f of the 132 declaration filed on December 19, 2004. Consequently, the prior art offers no suggestion or expressed

expectation that administration of allopregnanolone would successfully treat a traumatic brain injury.

The Examiner continues to assert that "allopregnanolone is also known to possess higher potency and efficacy than progesterone" based on the teachings of Gee *et al.* (page 8, lines 16-17 of the Office Action mailed April 21, 2004). Applicants disagree with this assertion. As outlined in section 4a of the 132 declaration, Gee *et al.* teach that both progesterone and many of its metabolites bind with high affinity to a unique GABA/GBR complex and that these metabolites delay onset of myoclonus following TBPS induced seizures in mice. There is no data demonstrating that progesterone and allopregnanolone are effective at treating other disease states, such as traumatic brain injury, and certainly no teaching that *all* of progesterone's beneficial effects are related to progesterone's conversion into its various metabolites.

The Examiner continues to assert that allopregnanolone and progesterone have the "the same therapeutic usefulness" (emphasis in original, page 8, lines 21-22 of the April 21, 2004 Office Action). As discussed above, the Examiner has failed to satisfy the requirements of MPEP 2144.02 and 2144.03 and provide evidence for these conclusions. The Examiner's attention is drawn to sections 4e of the 132 declaration that outlines that the mechanism of action by which progesterone and allopregnanolone mediate their neuroprotective effects is unknown and further concludes that one of skill would not assume progesterone and allopregnanolone have identical mechanisms of action.

As previously made of Record, pages 20-32 of the instant specification demonstrates for the first time that following a traumatic central nervous system injury, the administration of allopregnanolone significantly reduces cerebral edema when compared to control rats (See Figure 1); significantly increases the learning rate compared to control rats (See Figure 2); and, significantly delays the synthesis and level of activity of inflammatory cytokines (Figures 3 and 4). The Examiner, however, states that the results set forth in the specification of the instant invention are not unexpected based on the cited prior art and therefore concludes that a reasonable expectation of success exists. The Examiner is reminded that one cannot base obviousness upon what a person skilled in the art might try or might find obvious to try but rather must consider what the prior art would have led a person skilled in the art to do. As discussed above, Gee *et al.* teaches that progesterone and its metabolites have varying activity

and offer no teaching that allopregnanolone could treat a *traumatic* injury to the CNS. Similarly, Roof *et al.* only teach the administration of allopregnanolone following a frontal contusion. Prior to the present invention, one of skill in the art would not have recognized that allopregnanolone could be used to treat a traumatic CNS injury or decrease neurodegeneration as claimed by the present invention. Therefore, contrary to the Examiner's assertion, there was not a reasonable chance of success.

Moreover, the Examiner continues to maintain that since Examples 6 and 7 of the present application administer progesterone, the "Applicant clearly acknowledges that progesterone and its particular metabolite, allopregnanolone, have the same therapeutic usefulness" (page 9 of the Office Action dated April 21, 2004). ***Applicants never stated or suggested that progesterone and allopregnanolone have the same therapeutic usefulness.*** The examples using progesterone simply provide further evidence of the activity of progesterone on behavior and lesion size and the use of a cyclodextrin vehicle in administration. These experiments do not indicate that the results should be extrapolated to allopregnanolone. Examples 6 and 7 do not represent examples of the invention presently being claimed, and the Examiner is respectfully requested to withdraw her assertion regarding Applicant's admission. *If this assertion is maintained, the Examiner is respectfully requested to cite the authority for this conclusion.*

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CONCLUSIONS

In view of the foregoing remarks, Applicants respectfully submit that the rejection of claims 1-20 under 35 U.S.C. §103 is overcome. Accordingly, Applicants submit that this application is in condition for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Pamela Lockley 9/21/04
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